Amendments to the specification:

All of the specification amendments are content taken from the related Provisional Application No. 60/319,436 and had been pasted here.
Here bold, italics were added (that to the applicant's understanding would not be shown in the PTO publication). ... indicates parts deleted for brevity (but if the examiner wishes the whole part without deletion can be amended).

Please add the following new paragraphs before the paragraph on page 18 that begins with "whereas particular embodiments of this invention",

but please add these paragraphs without the guidance numbering shown in the boxes, that had been displayed here so that we can reference these guidance to you in our reply.

Guidance 1a) [*for use* ***risk/benefit (side effect) analysis****, and other guidance*]: (starting at PTO page 31of 88: 0226 line 5 on – till 0229 first senence; 0229 line 20 – line 42; 0230:

As in all treatment, the final decision is (always) up to the patient and the treating clinician. Offering to our patients more than one options that include the combination use of psychotropic medications can show many advantages. With this we are involving them in the decision-making, but we are supposed to discuss with them the *risks/benefits*, side effects of the medications, and *available alternatives* anyway.
If the patient opts to take only one medication, an antidepressant, let's work with him or her. But if the patient (as usual) is 'tormented' by the depression or depression and anxiety, or has a suicidal ideation, hopelessness, or (after we educate them) expects/wishes an "immediate" improvement, ...we should **put more weight on the use of medication combination** (preferably by adding an atypical neuroleptic or a "dopamine system stabilizer").
In psychiatry we are not afraid of prescribing more than one medications to our patients, and the treatment of depression should not be an exception.
The treatment of depression can be started right away with more than just one medication, the antidepressant....

Predicting which patients will commit suicide is an impossible task, and there are no models of suicide risk assessment that had been empirically tested for reliability and validity. (Simon, R.I., 2002.) It is often difficult for the clinicians to assess the risk of suicide systematically, due to the large volume of the patients, and due to the limited time and resources. The information being available is often limited. There is a continuum in the risk assessment from only asking the patients if they are suicidal, to performing formal systematic suicide risk assessment. It had been admitted even in academic publications that the former is much more common. (Simon, R.I., 2002.) Unfortunately, according to Simon, the "no harm contract" is unreliable, and short hospital length of stay, rapid patient turnover, brief outpatient and partial hospitalization visits, and the split treatment in managed care setting, results in difficulties and that the suicide risk factors are usually not recognized by the clinicians. (Simon, R.I., 2002.) Only the sickest patients are admitted to inpatient psychiatric units, (Simon, R.I., 2002), and the average length of

stay (median) for depression/mood disorder can be as little in some (multi-county US) geographical areas as six days. (Mode: 4 days). The length of stay for patients whose medication need to be adjusted may actually be even less, as patients requiring ECT take off from the average hospital days from the former group. (Depression and other mood disorders in Southwestern Pennsylvania). The assessment of suicide is further complicated by the fact that approximately 25% of patients at suicide risk do not admit to being suicidal. (However, in most cases they had communicated suicidal ideation or intent to family members.) (Fawcett cit#18. < also referenced in: Simon, R.I., 2002). Patients, who deny suicide risk, usually do not meet Managed Care criteria for hospitalization. ...

The above paragraph summarizes the challenges that both patients and clinicians face. ...

Guidance 2a) [*The importance for the clinician of looking at the benefit of the group (as it also has the benefit for the individual)*]: starting at PTO page 34of 88: 0232- till 0234 line11; 0234 line 15- till 0234 line 25:

We have to balance the risk / benefit of our intervention both for the individual patient and for the group of patients we are treating. This had been customary for long, in the medical practice.
A good example for this is of how we were treating appendicitis. If the patient showed some typical symptoms that he or she *might* have appendicitis (specifically if the WBC was also elevated), then the surgeon was operating on. The surgeon had rather operated on healthy people for whom it turned out on the operating table that they did not had an infected appendix, (taking out the appendix anyway), then wait until it became obvious that the appendix had perforated. This is quite a standard procedure that surgeons followed. The risk of dying from the operation (without an infected appendix) was far less compared to waiting and having the (high) risk of death from operating late with a perforated appendix.
The clinicians have a responsibility of not only weighting the risk of the individual but also the risk of a group.
We are following similar procedures and we give thiamin routinely for everybody in the emergency room before giving IV glucose, (therefore preventing Korsakov's syndrome in alcoholics).
We are routinely testing for drug screen in the ER (and the patient gets charged for the cost); even when the patient says that he or she is absolutely not taking any illicit drugs. This is a standard procedure and good clinical practice. The risk of being operated on or getting a blood or urine drug screen is not the same. Nevertheless, we take into account the risk/benefit for a group not just for an individual. So why are we not more vigorous in preventing suicide? We are not saying that we should blindfoldedly prescribe a combination of psychotropic medication for every depressed person against their will, but to discuss the *risks / benefits* and *alternatives* with the patients as we mentioned it above. ...

(One could speculate that if using the SSRI-atypical neuroleptic combination would increase the response rate of treatment-resistant depression, then the percentage rate for improvement would be also higher if given for everybody who is clinically depressed, that is without separating the 'responders' from the 'non-responders'.

This speculation is probably correct, **but by itself would not substantiate the added risk using the neuroleptics.** With this rationale, the two step strategy would seem still to be the logical step, to treat the depressed patients with antidepressants first, and reserve other strategies for the treatment-resistant group only. In the argument to consider, or start using the combination treatment right away in all those who are clinically depressed, it is the decrease of suicide rate that is the paramount important factor. ...

Guidance 2b) [*comparing (as reason to use our method) the suicide rates of MDD and Borderline Personality Disorder (BPD)*]: starting at PTO page 22 of 88: 0200 – till 0203.

It had been noted that in assessing suicide the focus should be on the characteristics of those who commit suicide rather than on the characteristics of patients with suicidal ideation. (Forster P., 1994.) The same article also notes that major depression is associated with the largest number of completed suicide and half or more of all who commit suicide qualify for this diagnosis. About 15% to 20% of all patients with serious affective disorder will kill themselves. (Forster P., 1994.).

On the other hand 8% of borderline personality disorder (BPD) patients will commit suicide. (Forster P., 1994. – cit#21.). BPD is a separate diagnostic category from major depressive disorder and not even listed under the mood disorder category (See DSM-IV-TR.). It is also known that in treating borderline personality disorder (BPD), we are using "all of the available psychotropic medications, and combinations of them". (See also Gabard's video 9/11/1992, – and published by APAin 1995, Markovitz, P. J. et al. 1991, **versus patent** # 5,589,512 on BPD filed January 1994,). It is true, depression is only one of the comorbid conditions associated with BPD, some others being rejection sensitivity and cognitive distortions to the extent of "mini psychosis" (See also Gabard's video 9/11/1992, – and published by APA 1995). (For diagnostic criteria please refer to DSM-IV TR.)
Our point is that with this disorder we were not afraid of using the combination of antidepressants with antipsychotic medications or even adding a mood stabilizer. Yet in major depressive disorder; in serious affective disorder *with 2-2 ½ times more risk for committed suicide*, we continue to refrain from using or even trying this combination.
In BPD at times we are even using clozapine (Clozaril) despite for its high risk for agranulocytosis and despite that it had been prohibitively costly, due to the need of weekly or biweekly blood draws (Frankenburg, et al. 1993). We are not recommending Clozaril to treat major depression or other depressive disorders, ...when other much safer (and cheaper) atypical antipsychotic medications are now on the market. However, we do advocate taking a closer look, and considering using the "new generation atypical neuroleptics" or the even newer "dopamine system stabilizers" together with the antidepressants.

What is deceptive at the first look is, that patients with BPD may show more frequent suicidal gestures and may struggle with almost constant suicidal ideation, but the fact remains that the risk of committing suicide is still 2-2 ½ times more in people with serious affective disorder then in BPD. [For the statistics of suicide risk, please see: (Forster P., 1994.)]

For us in the medical profession it would not be fair to continue hiding under the excuses of the added risk of the potential side effects of the antipsychotic medications, specifically with the availability of some of the safer atypical antipsychotics.

Guidance 1b) [*further guidance on* ***risk/benefit (side effect) analysis***]: starting at PTO page 35 of 88: 0236 line 4 – 0238; 0240:

One of the major concern about to use a neuroleptics had been their potential side effects. Although even with the traditional antipsychotics the development of neuroleptic malignant syndrome (with fever, rigidity, and increase in creatine phosphokinase - CPK) had been rare, but this syndrome is potentially lethal. Now that the psychiatrists are more aware of that syndrome they may be able to intervene and start treating it early with better outcomes. In addition and more importantly, the development of neuroleptic malignant syndrome (NMS) may be diminished with atypical antipsychotics. (Caroff, S. N. et al. 2002.).
Another concerning side effect is tardive dyskinesia that has a prevalence among individuals treated with traditional antipsychotics that range from 10% to 15% in young patients, and 12% to 25% in chronic patients. It is has been estimated that up to 90 percent of the cases of tardive dyskinesia goes unrecognized even in academic residency training impatient units. (Rotrosen, J., et al. 1995.). …

Although written consent for neuroleptics are not required for outpatient setting, many large institutions adapted such a policy. The side effect profile of atypical antipsychotics is so much less, that in a health system that is a part of a major chain of medical and psychiatric / inpatient and outpatient services, a meeting was held, where the issue of abandoning their *written* consent form for TD/NMS was seriously considered. (Written communication).

Guidance 3) [*Rule of thumbs; guidance for how long to use the antipsychotic*]: starting at PTO page 48 of 88: 0286-0288:

The issue of how long one should take an antidepressant needs to be discussed with the patient. There are only general guidelines for this. The "rule of thumb" varies by how many times the patient relapsed (possibly also taking into account the family history), the patient's age, and (with the newer safe antidepressants) if the patient wants to risk a relapse. These guidelines are known to the clinicians.

Since there are no data on starting the treatment of depression right away with the combination of psychotropic medications, no definitive guidance can be given on **how long one should continue to take the neuroleptic**. The only data we can rely on comes from treating psychotic depression and from the sporadic case reports in the treatment of refractory depression. In some of the case reports when either the patient run out of risperidone over the weekend (Kaplan, M. 2000), or when 3 weeks later it was discontinued (O'Connor, M., et al 1998) the patients anxiety or agitation **returned**. Again these were *treatment-resistant depression*. The reinstated medication (neuroleptic) came with an immediate relief. For other patients taking risperidone for 2 weeks or 3 months, the discontinuation of the added neuroleptic did not cause deterioration few weeks later (O'Connor, M., et al 1998). Parker, G., et al. (2002) reports that they have treated treatment-resistant non-psychotic depression, and one of their patients presented in a case report improved with the addition of olanzapine, and worsened when it was tapered off. The same response was observed when the atypical antipsychotic was reinstated, or again tapered. Pitchcot, W., et al. (2001) reports that their patient with a long history of treatment-resistant non-psychotic depression improved moderately on venlafaxine but on 5 mg of added olanzapine experienced a marked improvement with a complete remission. However, when olanzapine was stopped due to it's side effect causing weight gain, the patient experienced a new depressive symptom after 4-5 days. Taking the olanzapine again, the patient experienced a dramatic antidepressant response again, maintaining the full remission for 15 months [continuing with the medication combination].

Since TD is still a concern with the atypical neuroleptics, it is fair to say that we should follow a similar 'rule of thumb' then with beztropine: that is to **reassess** the patient in a few weeks and again in a few months, and attempt to discontinue it if clinically indicated, and the patient is doing well. If symptoms reoccur, that will shift the clinician's decisional balance to reinstate the neuroleptic. *For psychotic depression some recommended using the **neuroleptic for one year*** **as the depressive relapse is high otherwise**. (Keck, P.E. et al. 2000 (a),). Time and experience with this medication combination will teach us more. The patient's history for suicidality, (suicidal risk factors), impulsivity, 'near-paranoia', comorbid disorders (anxiety, alcohol or substance abuse/dependence, personality disorders), or strong cognitive distortions may also guide the clinician toward continuing with the more vigorous treatment of depression with the combination of psychotropic medications.

Additional references from the provisional as relates to the above guidance:

Caroff, S. N. eat al: Movement disorders associated with atypical antipsychotic drugs. J. Clin. Psychiatry. 2002; 63 (suppl 4) 12-19.

Fawcett cit#18: Please see citation 18 referenced in: Simon, R.I., 2002

Forster P. Accurate assessment of short term suicide in a crisis. Psychiatric Annals 24:11, 1994 571-578.

Frankenburg, F.R. et al. Clozapine treatment of borderline patients: a preliminary study. Compr. Psychiatry. 1993, 34:402-405.

Gabbard, O.G. Integrated treatment of borderline personality disorder: Pharmacotherapy and psychotherapy. (video) 1995, American Psychiatric Press.

Keck, P.E. et al.(2000 a) Antipsychotics in the treatment of mood disorders and risk of tardive dyskinesia. J. Clin. Psychiatry, 2000, Suppl. 4. 33-38.

Rotrosen, J., et al: The importance of Side effects in the development of new antipsychotic drugs. Psychiatric Annals. 25:5, 1995, 306-310.

Simon, R.I., Suicide risk assessment in Managed Care settings. Primary Psychiatry, April 2002; Vol 9. NO.4. 42-49.

The Pennsylvania Health Care Cost Containment Council. Depression and other mood disorders in Southwestern Pennsylvania. July 2001. 1-169.